REMARKS

These remarks are in response to the final Office Action mailed November 18, 2003. Claims 1 to 51 are pending. Claims 13 and 15 to 47 stand withdrawn from consideration as directed to an unelected invention. Claims 1 to 12, 14 and 48 to 51 are therefore under consideration. Applicants respectfully request reconsideration of the present application.

Regarding the Objection to the Disclosure

The disclosure stands objected to due to the arrangement of the specification and the drawings. Applicants respectfully request that the objection be held in abeyance until such time allowable subject matter is indicated. Applicants will then submit corrections to the specification or a substitute specification, as appropriate, and corrected drawings in compliance with the draftsperson's review.

Regarding the Drawings

The drawings stand not approved. Submitted herewith are seven sheets of formal drawings for Figures 1 to 4. Applicants respectfully request that the drawings be accepted.

I. REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

The rejection of claims 1 to 5, 7, 9 to 12, 14, 48, 50 and 51 under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement is respectfully traversed. The Examiner maintains that the specification allegedly does not enable the full scope of the claims.

The specification adequately enables the claims for the reasons of record and as set forth in detail below. In order to correct the record, several inaccurate statements in the Office Action must first be addressed. The following remarks address these statements as well as address the grounds for rejection.

The first inaccurate statement is that, according to the Office Action, allegedly "[c]laims 1-3 encompass any base change in any nucleic acid molecule such as mRNA and genomic DNA and any amino acid substitution in positions such as 2-16, 114-149, 179-225 or/and 267 to 397 and any gene conversion involving exons 6 to 9 which are replaced by the corresponding exons of the RHCE gene." [page 6, Office Action] To the contrary, claim 1 recites a "nucleic acid molecule encoding a human Rhesus D antigen contributing to or indicative of the weak D

phenotype, said nucleic acid molecule carrying at least one missense mutation, as compared to the wild type Rhesus D antigen set forth as SEQ ID NO:41, in its transmembrane and/or intracellular regions." Claim 2 recites a "nucleic acid molecule carrying at least one missense mutation, as compared to the wild type Rhesus D antigen set forth as SEQ ID NO:41, in amino acid positions 2-16, 114-149, 179-225 or/and 267 to 397 with the proviso that said D antigen does carry not a single missense mutation leading to a substitution of phenylalanine in amino acid position 223 by valine or of threonine in position 283 by isoleucine; or carrying a gene conversion involving exons 6 to 9 which are replaced by the corresponding exons of the RHCE gene." Claim 3 recites "[t]he nucleic acid molecule of claim 1 or 2 a wherein said missense mutation causes an amino acid substitution in position 3, 10, 16, 114, 149, 182, 198, 201, 220, 223, 270, 276, 277, 282, 294, 295, 307, 339, 385 or 393 or a combination of said substitutions." Thus, claims 1 to 3 clearly do not encompass any base change in any nucleic acid molecule, or any amino acid substitution in positions such as 2-16, 114-149, 179-225 or/and 267 to 397 and any gene conversion involving exons 6 to 9, which are replaced by the corresponding exons of the RHCE gene.

Another inaccurate statement is that, according to the Office Action, "the nucleic acid molecule in amended claims 1 and 2 still encompass any missense mutation." [page 9, Office Action] Again, for the reasons set forth above, claims 1 and 2 cannot be said to "encompass any missense mutation"

Yet another inaccurate statement is that, according to the Office Action, "the claim [claim 14] encompasses any random sequence such as any oligonucleotide that is 12 to 50 or 15 to 24 nucleotides in length." [page 8, Office Action] To the contrary, claim 14 recites an "oligonucleotide hybridizing under 0.1X SSC, 0.1% SDS at 65^0 C hybridization and washing conditions to a portion of the nucleic acid molecule of any one of claims 1 or 2 comprising said at least one missense mutation or to the complementary portion thereof or hybridizing to a region involving the breakpoint of the gene conversion identified in claim 2." Thus, clearly the oligonucleotides encompassed by claims 14 and 48 do not include any random oligonucleotide that is 12 to 50 or 15 to 24 nucleotides in length.

Claims 1 to 5, 7, 9 to 12, 14, 48, 50 and 51 are adequately enabled by the specification. As set forth in Applicants previous responses, the specification teaches how to make and use the

claimed nucleic acid molecules, vectors, host cells, kits and methods without undue experimentation.

First, as previously pointed out the human RHD gene is highly conserved among humans. Generally, in humans having an intact RHD gene, nucleotide sequence homology exceeds 90%, more typically 99% or greater. Thus, given the extent of homology, the nucleic acid molecules encoding human RhD are readily identifiable by comparing sequences.

Second, the nucleotide sequences of other human RHD alleles that contribute to or are indicative of the weak D phenotype can be easily identified using routine techniques disclosed in the specification or known in the art at the time of the invention. For example, the specification discloses that blood samples may be analyzed for expression of antigen D using PCR-RFLP (page 28, lines 5-9). To identify nucleic acid molecules with missense mutations, the specification discloses that samples with weak D expression can be analyzed for missense mutations by nucleotide sequencing or by PCR-RFLP or RH PCR-SSP (see, for example, page 8, lines 17-24, and page 29, lines 9-25). To identify RHD gene conversion involving exons 6 and 9 replaced with the corresponding region of RHCE gene, the specification discloses that samples with weak D expression can be analyzed by sequencing with primers specific for RHCE and RHD; detecting the presence of RHCE sequences in the RHD gene indicates the presence of the gene conversion (page 29, line 25, to page 30, line 5). Nucleotide sequencing, PCR-RFLP and RH PCR-SSP that detect sequence mutations, among other assays for detecting RHD gene alleles (e.g., Smythe *et al.*, Blood 87:2968 (1996), submitted herewith as Exhibit 1) were all known in the art and routine at the time of the invention. The skilled artisan can subsequently clone any of the identified RHD alleles using routine molecular biological techniques in order to obtain nucleic acid molecules encoding a human Rhesus D antigen contributing to or indicative of weak D phenotype. Thus, the skilled artisan could readily identify and obtain additional nucleic acids encoding human Rhesus D antigen that contribute to or are indicative of the weak D phenotype without undue experimentation.

Third, the specification teaches the location of numerous missense mutations of human RHD located in the transmembrane and/or intracellular regions. In particular, the specification exemplifies 21 different nucleic acid molecules having missense mutations that encode a human Rhesus D antigen contributing to or indicative of a weak D phenotype. Thus, in view of the guidance in the specification, the skilled artisan would know that the transmembrane or

intracellular region of RHD are likely candidates for a missense mutation, and would therefore also know to look in these regions in order to identify mutations that contribute to or are indicative of the weak D phenotype. Consequently, given the guidance in the specification and knowledge in the art, it cannot objectively be said that it would require undue experimentation to identify other human RHD alleles that contribute to or are indicative of the weak D phenotype.

Fourth, the statement in the Office Action as to "which base change or substitution (claim 1) in a codon that cause insertion of a different amino acid (missense mutation) in the transmembrane and/or intracellular regions of the human Rhesus D antigen encoded by SEQ ID No:41 and whether the resulting nucleic acid molecule maintains its structure and function as SEQ ID NO:41" or "which amino acid in amino acid positions such as the ones recited in claim 2 be substitute for which undisclosed amino acid (claim 2) the would maintain the same structure and function as SEQ ID NO:41," evidences a misunderstanding of the invention. [page 7, Office Action; see, also, page 9] First, it is not necessary that the claimed nucleic acid molecules maintain the structure or function of a protein encoded by SEQ ID NO:41. Second, it is not necessary to know the amino acid positions, such as the ones recited in claim 2, that can be substituted and maintain the same or function of a protein encoded by SEQ ID NO:41. There is simply no requirement that the claimed nucleic acids encode a protein with amino acid changes that maintain the structure or function of SEQ ID NO:41 because the claimed nucleic acid molecules are useful in themselves to screen for the weak D phenotype (see, for example, page 13, last paragraph; and the paragraph bridging pages 14 and 15). Thus, as the claimed nucleic acid molecules can be made and used without encoding a functional protein, they need not maintain a structure or function of wild type Rhesus D antigen set forth as SEQ ID NO:41. Consequently, the ground for rejection relating to a purported need for amino acid changes to maintain the structure or function of SEQ ID NO:41 is not applicable to enablement of the claimed nucleic acid molecules, vectors, host cells, kits and methods.

Likewise, the cited Stryer *et al.*, Ngo *et al.* and Skolnick *et al.*, references are not applicable to enablement of the claimed nucleic acid molecules, vectors, host cells, kits and methods. In this regard, each of these references generically relate to the effect of amino acid changes on protein structure or function. Again, however, the claimed nucleic acid molecules encoding human Rhesus D antigen contributing to or indicative of weak D phenotype are useful in themselves and, therefore, need not encode a protein with the structure or function of SEQ ID

NO:41 in order to be useful. Consequently, the Stryer *et al.*, Ngo *et al.* and Skolnick *et al.* references are also not applicable to enablement of the claimed nucleic acid molecules, vectors, host cells, kits and methods.

In sum, in view of the specification which discloses routine assays for identifying nucleic acid molecules encoding a human Rhesus D antigen contributing to or indicative of weak D phenotype and the location in the Rhesus D gene where such mutations may occur, and further in view of the fact that routine assays for identifying and obtaining nucleic acid molecules were known in the art at the time of the invention, the skilled artisan could readily make and use other human Rhesus D antigens contributing to or indicative of weak D phenotype without undue experimentation. As such, claims 1 to 5, 7, 9 to 12, 14, 48, 50 and 51 are adequately enabled and the rejection under 35 U.S.C. §112, first paragraph, is improper and must be withdrawn.

The rejection of claims 1 to 5, 7, 9 to 12, 14, 48, 50 and 51 under 35 U.S.C. §112, first paragraph, as allegedly lacking an adequate written description, is respectfully traversed. The Examiner maintains that allegedly the specification does not provide an adequate written description of the claimed nucleic acid molecules, vectors, methods, oligonucleotides and kits.

In order to satisfy the written description requirement under 35 U.S.C. §112, first paragraph, the Federal Circuit explained that, with respect to a genus of nucleic acids, a "description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus ***or*** of a recitation of structural features common to the members of the genus, which constitute a substantial portion of the genus." *Reagents of the Univ. Calif. v. Eli Lilly* 119 F.3d 1559, 1568 (Fed. Cir. 1997), *Emphasis added.* Although the courts have not specified how many species constitute a representative number, the courts have stated that "every species in a genus need not be described in order that a genus meet the written description requirement" and "Applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art." *Id.*, see, also, *In re Angstadt*, 537 F.2d, 498, 502-503 (CCPA 1976). Thus, clearly a description of all species of human Rhesus D antigen contributing to or indicative of weak D phenotype need not be described in order to satisfy the written description requirement under 35 U.S.C. §112, first paragraph. Rather, what is required is a "a representative number" **or** "a

recitation of structural features common to the members of the genus, which constitute a substantial portion of the genus."

Here, the specification discloses a representative number of nucleic acid molecules encoding human Rhesus D antigen contributing to or indicative of a weak D phenotype species to adequately describe a genus of nucleic acid molecules encoding human Rhesus D antigen contributing to or indicative of a weak D phenotype species. Again, the specification exemplifies 21 different nucleic acid molecules that encode a human Rhesus D antigen contributing to or indicative of a weak D phenotype. In particular, the different nucleic acid molecules encoding RHD genes have missense mutations at positions 8, 29, 48, 340, 446, 544, 594, 602, 658, 667, 809, 819, 826, 830, 845, 880, 885, 919, 1016, 1154 and 1177. In addition, an RHD gene conversion in which exons 6 to 9 have been replaced with the corresponding exons of RHCE that contributes to or is indicative of the weak D phenotype is also disclosed. Thus, in view of the fact that the specification discloses a large number of different nucleic acid molecules that encode a human Rhesus D antigen contributing to or indicative of a weak D phenotype, a representative number of species for the genus of nucleic acid molecules encoding human Rhesus D antigen contributing to or indicative of a weak D phenotype is provided.

Furthermore, structural features common to a substantial portion of the genus of the human RHD alleles, which include features common to a substantial portion of the genus of nucleic acids encoding Rhesus D antigen contributing to or indicative of a weak D phenotype, are discussed above and in the record. For example, the sequence of several human RHD alleles was known at the time of the invention and human RHD is highly conserved among humans that have the gene. As evidence that numerous RHD alleles were known at the time of the invention, Flegel *et al.* (Transfus. Med. 8:281 (1998)) was previously submitted as Exhibit A (see, for example, Table 4, which lists PCR setups for detecting numerous particular RHD alleles). As additional evidence that human RHD sequences were known at the time of the invention, submitted herewith as Exhibits 1 and 2, are publications by Smythe *et al.* (Blood 87:2968 (1996)) and Suyama *et al.* (Blood 84:1975 (1994)), respectively. Each of Exhibits 1 and 2 describe RHD nucleic acid sequences (see, for example, Exhibit 2, page 1978, Fig. 4). Thus, given the numerous RHD sequences known at the time of the invention and the high homology of human RHD sequences, one skilled in the art would know structural features common to a substantial portion of the genus of human RHD sequences, as well as structural features common

to a substantial portion of the genus of nucleic acids encoding Rhesus D antigen contributing to or indicative of a weak D phenotype.

Finally, as to the grounds for rejection in the Office Action relating to oligonucleotides, allegedly that "there is inadequate description about the structure (nucleotide sequence) of said oligonucleotide," Applicants once again point out that the specification exemplifies 21 different nucleic acid molecules that encode a human Rhesus D antigen contributing to or indicative of a weak D phenotype, that numerous RHD sequences were known at the time of the invention, and that human RHD sequences exhibit high homology. Consequently, the skilled artisan would know or could readily predict the oligonucleotides that would hybridize to the claimed nucleic acid molecules under the recited conditions. Furthermore, particular examples of oligonucleotides that specifically hybridize are exemplified in the specification, for example, SEQ ID NOs: 3, 4, 7, 16-18, 20, 23, 25, 26 29, 30, 39 and 40. Thus, in view of the foregoing, an adequate written description is provided for the oligonucleotides and kits of claims 14 and 48, respectively.

In sum, in view of the specification, which discloses 21 different nucleic acid molecules encoding a human Rhesus D antigen contributing to or indicative of a weak D phenotype, and that the probable location of missense mutations will be in the transmembrane or intracellular region, a representative number of nucleic acid species encoding a human Rhesus D antigen contributing to or indicative of a weak D phenotype is provided. Further in view of the fact that numerous RHD sequences were known and that RHD sequences exhibit high homology, one skilled in the art would know structural features common to a substantial portion of the genus of human RHD sequences, as well as structural features common to a substantial portion of the genus of nucleic acids encoding Rhesus D antigen contributing to or indicative of a weak D phenotype and, therefore, the skilled artisan would be apprised of the genus nucleic acid molecules encoding Rhesus D antigen contributing to or indicative of a weak D phenotype. As such, an adequate written description of nucleic acid molecules encoding Rhesus D antigen contributing to or indicative of a weak D phenotype is provided. Consequently, the rejection under 35 U.S.C. §112, first paragraph as allegedly lacking an adequate written is improper and must be withdrawn.

II. REJECTIONS UNDER 35 U.S.C. §102 and 103(a)

The rejection of claims 2 and 9 under 35 U.S.C. §102(b) as allegedly anticipated by Rouillac *et al.* (Am. J. Hematol. 49:87 (1995)) is respectfully traversed. The Examiner indicates that Rouillac *et al.* allegedly describe "a polynucleotide that encodes a human Rhesus D antigen such as Rh40 carrying one missense mutation at nucleotide position 329 from T to C that results in amino acid substitution from leucine to proline substitution at position 110 which is within the 114-149 of the RhD polypeptide compared to the wild type sequence of the claimed SEQ ID NO:41." [see Office Action, page 15, section 7]

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration (*In re Spada*, 15 USPQ 2d 1655 (Fed. Cir. 1990), *In re Bond*, 15 USPQ 2d 1566 (Fed. Cir. 1990).

Rouillac *et al.* do no teach or suggest claims 2 or 9. Claim 2 is directed to a nucleic acid molecule encoding a human Rhesus D antigen contributing to or indicative of the weak D phenotype carrying at least one missense mutation, as compared to the wild type Rhesus D antigen set forth as SEQ ID NO:41, in amino acid positions 2-16, 114-149, 179-225 or/and 267 to 397, with the proviso that the D antigen does carry not a single missense mutation leading to a substitution of phenylalanine in amino acid position 223 by valine or of threonine in position 283 by isoleucine; or carrying a gene conversion involving exons 6 to 9 which are replaced by the corresponding exons of the RHCE gene. In contrast, Rouillac *et al.* describe a D^{VII} blood group antigen, which is not a weak D phenotype. Furthermore, the D^{VII} blood group antigen described by Rouillac *et al.* is located at position 110 (T329C, see abstract, and page 88, first column), which is not a position within the recited amino acid positions 2-16, 114-149, 179-225 or/and 267 to 397 of claim 2. Accordingly, as Rouillac *et al.* fail to describe or suggest the nucleic acids of claims 2 or 9, the rejection of claims 2 and 9 under 35 U.S.C. §102(b) over Rouillac *et al.* (Am. J. Hematol. 49:87 (1995)) is improper must be withdrawn.

The rejection of claims 1, 3, 4, 5, 9, 12, 50 and 51 under 35 U.S.C. §102(a) as allegedly anticipated by Legler *et al.* (Transfusion 38:434 (1998)) is respectfully traversed. The Examiner indicates that Legler *et al.* allegedly describe "a polynucleotide that encodes a human Rhesus D antigen contributing to or indicative of the weak D phenotype...." [see Office Action, pages 15 and 16, section 8]

The cited Legler *et al.* reference was published in May 1998. In contrast, the subject application has a priority date of January 23, 1998. Accordingly, Legler *et al.* is not available as prior art against any claims of the subject application. As such, the rejection under 35 U.S.C. §102(a) over Legler *et al.* (Transfusion 38:434 (1998)) is improper and must be withdrawn.

The rejection of claims 2, 9 and 14 under 35 U.S.C. §102(b) as allegedly anticipated by Avent *et al.* (Blood 89:2568 (1997)) is respectfully traversed. The Examiner indicates that Avent *et al.* allegedly describe "a nucleic acid molecule encoding human Rhesus D antigen contributing to or indicative of the weak D phenotype carrying a gene conversion involved exons 6 to 9...." [see Office Action, page 16, section 9]

Avent *et al.* do no teach or suggest claims 2, 9 or 14. Rather, Avent *et al.* describe D^+, D^- and partial D phenotypes, which are not weak D phenotypes. In this regard, the Examiner's attention is directed to Avent *et al.*, Table 1, page 2572. Table 1 is a list of D variants within the D^+, D^- and D^u/D^- variant phenotypes. Seventeen out of a total of 19 are partial D phenotypes, which are not weak D phenotypes (see Avent *et al.*, page 2575, second column: "Weak D phenotypes are not partial D phenotypes."). One of the remaining two phenotypes, namely D^uCcee (n=35) partial D phenotype, is exon 10 positive in all 35 samples and intron 4 positive in 31 out of 35 samples (see Table 1). D^uccEe (n=9) partial D phenotype, is also exon 10 positive and intron 4 positive in all nine samples. Because the 31 samples of D^uCcee and the nine samples of D^uccEe are exon 10 positive and intron 4 positive they have wild type exons 4 and 10. Consequently, these particular D^uCcee and D^uccEe samples are not RhD variants having a missense mutation, as required by claims 2, 9 and 14.

The remaining four D^uCcee (n=35) phenotypes that are exon 10 positive and exon 4 negative are also partial D phenotype. In support of this position, Avent *et al.* state that "[i]t is possible that those weak D phenotype individuals who type as RHD intron 4 negative *are uncharacterized partial D phenotypes*." [see Avent *et al.*, page 2575, second column, *Emphasis added*]. Partial D phenotoypes are known to be distinct from weak D phenotypes. To corroborate that partial D phenotoypes are not weak D phenotypes, submitted herewith as Exhibit 3, is a book chapter by Daniels, G. (Human Blood Groups, Blackwell Science, Ch. 5, pp. 208-221). In Exhibit 3, the author states that "Weak D red cells are considered to have all epitopes of D, expressed weakly. Partial D red cells have some epitopes missing, the remainder

being expressed normally." (page 210, 5.6.2, left column) Thus, the four exon 10 positive and exon 4 negative D^{u}Ccee phenotypes described by Avent *et al.* do not contribute to or are indicative of weak D phenotype, as required of claims 2, 9 and 14.

As to the assertion that Figures 2 and 7 of Avent *et al.* illustrates a gene conversion of exons 6 to 9, which are replaced by the corresponding RHCE gene, to the contrary, Figure 2 illustrates the wild type sequence of RhD intron 4. Figure 7 illustrates partial D phenotypes which are not weak D phenotypes. Furthermore, none of the partial D phenotypes in Figure 7 have a gene conversion involving exons 6 to 9 of RhD replaced by the corresponding exons of RHCE. Consequently, Avent *et al.* do not describe a gene conversion of exons 6 to 9 of human Rhesus D antigen, which are replaced by the corresponding RHCE gene, contributing or indicative of the weak D phenotype.

In view of the foregoing, Avent *et al.* does not describe claims 2, 9 and 14. As such, the rejection under 35 U.S.C. §102(b) over Avent *et al.* (Blood 89:2568 (1997)) is improper and must be withdrawn.

The rejection of claims 1, 2 and 10 to 12 under 35 U.S.C. §103(a) as allegedly unpatentable over Rouillac *et al.* or Legler *et al.* or Avent *et al.* each in view of Sambrook *et al.* (Molecular Cloning, 1989, Cold Spring Harbor Laboratory, CSH, NY, Ch. 17) is respectfully traversed. The Examiner indicates that the secondary reference of Sambrook *et al.* adds the limitations missing from the primary cited references as to claims 10 to 1, 2 and 10 to 12, thereby allegedly rendering these claims obvious.

As set forth above, because Legler *et al.* was published after the January 23, 1998, priority date, Legler *et al.* is not available as prior art against any claims of the subject application. As such, Legler *et al.* can not be used as a reference under 35 U.S.C. §103.

As to Rouillac *et al.*, Avent *et al.* and Sambrook *et al.*, none of claims 1, 2 and 10 to 12 would have been obvious in view of these references alone, or in any combination, at the time of the invention. As set forth above, at most Rouillac *et al.* describe a D^{VII} blood group antigen, which is not a weak D phenotype, and Avent *et al.* describe D^{+}, D^{-} and partial D phenotypes, which are also not weak D phenotypes. Sambrook *et al.*, *inter alia*, do not teach or suggest a nucleic acid molecule encoding a human Rhesus D antigen, nor a nucleic acid molecule encoding a human RHD antigen having a missense mutation, and, therefore, do not provide that

which is missing from Rouillac *et al.* and Avent *et al.* Thus, none of Rouillac *et al.*, Avent *et al.* and Sambrook *et al.* alone or in combination teach or suggest the nucleic acid molecules, vectors or methods of claims 1, 2 and 10 to 12.

Absent the requisite teaching or suggestion, claims 1, 2 and 10 to 12 would not have been obvious in view of the combination of Rouillac *et al.*, Avent *et al.* and Sambrook *et al.* at the time of the invention. Accordingly, Applicants respectfully request that the rejection of claims 1, 2 and 10 to 12 under 35 U.S.C. §103(a) be withdrawn.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that claims 1 to 12, 14 and 48 to 51 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 509-4065.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-2212.

Respectfully submitted,

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